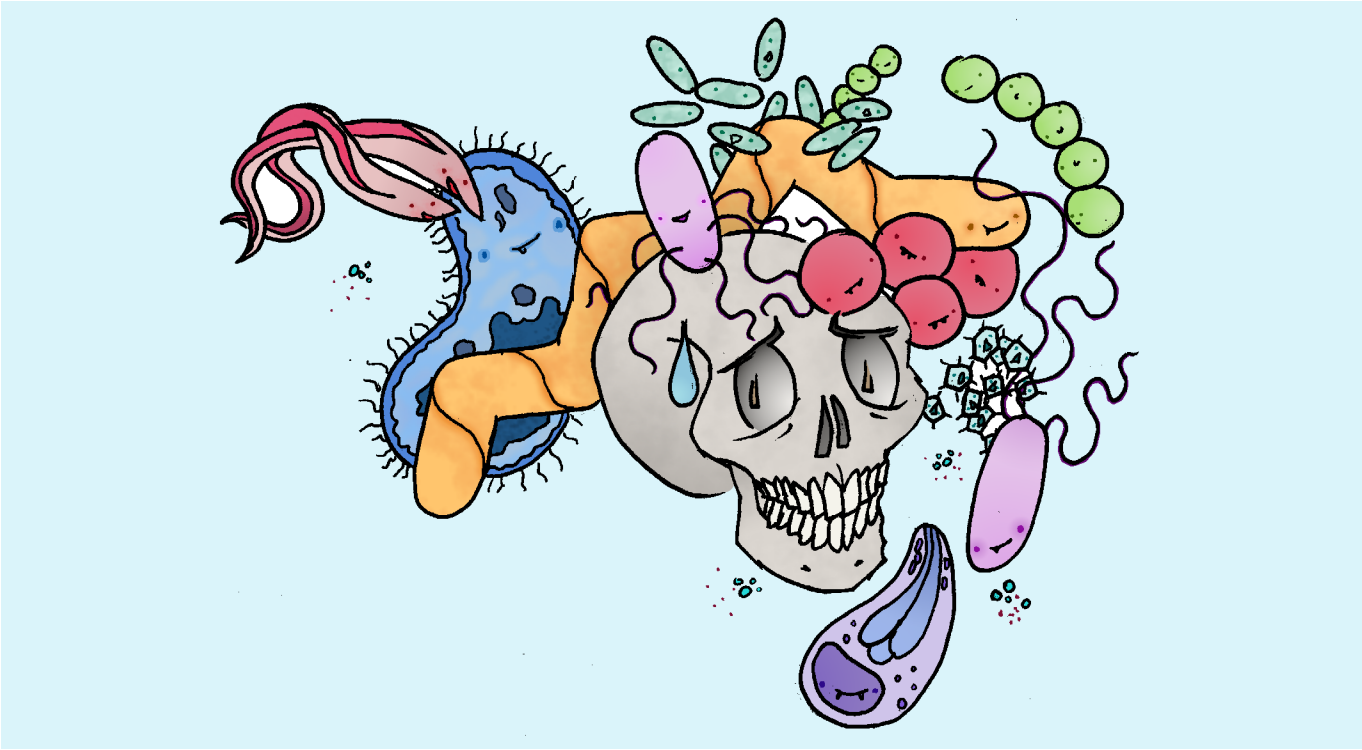

# IT'S THE MICROBES! HOW WE DISCOVERED THAT THE VILLAINS WERE MICRO-ORGANISMS

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BACTERIUM. Microscopic organism, composed of a single cell with no nucleus. Bacteria are all around us in the natural world; some of them can cause diseases, but most are benign.

VIRUS. A microbe that must infect a cell in order to multiply. Viruses are the cause of many diseases, both animal and human, and the best way to fight them off is through vaccination.

* see the glossary of infectious disease below

MICROBE. A term introduced by the French physician Charles Sédillot to designate the microscopic entities which can cause illnesses, discovered not too long ago, particularly by Pasteur.

It's common knowledge today that many diseases are caused by microscopic organisms (bacteria or viruses). It's hard to imagine, but just century and half ago we didn't know this. Even the word "microbe" didn't exist. Because we didn't know about microbes, we didn't understand the causes of certain diseases – like typhoid*, diphtheria* or polio*, which until their recent resurgence had been almost entirely eradicated from Europe, but which once killed countless young children. There were few families who didn't lose a child, or even several children, to one of these diseases. All that changed in the span of a few years around 1880. Micro-organisms, renamed as microbes, were discovered and identified as the causes of these diseases. This paved the way for the production of vaccines and sera to fight them. Now for the history of this revolution in medicine and some of the people who were essential to its success.

In 1850, people still thought that diseases were caused by "miasma" – a vapor that hung around in the air around bogs and marshes. Diseases had been blamed on "miasma" since ancient times. Even after micro-organisms were first observed through a microscope, it still took another two hundred years before they definitively replaced the "miasma" theory as the cause of certain diseases and epidemics.

* see the glossary of infectious disease below

Throughout all this time, people knew that diseases could spread person to person. People with leprosy* were sent to live outside the boundaries of towns and villages to prevent contamination, the spread of the virus. Furthermore, it was common knowledge that the bubonic plague*, which decimated Europe in the 14th century, had been introduced by ships that sailed in from the East, from countries where large numbers of people were infected by it. Victims of the bubonic plague were buried as quickly as possible in order to protect the rest of the population. People weren't quite sure what the bubonic plague was, but they knew it could be transmitted from plague-ridden corpses. Quarantine (40 days of isolation) was imposed on travelers from countries where contagious diseases were widespread. Gradually, sanitary measures were introduced: ventilation in houses and hospitals, hand-washing, and sewers and pipes for getting rid of effluent. However, there was little proof of their efficacy and imposing these sanitary measures cannot be justified.


In 1848, at the main hospital in Vienna, Austria, large numbers of women were dying soon after childbirth from something called puerpureal fever*, also known as childbed fever. Ignaz Semmelweis, a young Hungarian doctor, noticed that doctors were delivering babies straight after performing autopsies on women who had died from childbed fever, without even washing their hands. Childbirth mortality dropped dramatically when doctors were told to wash their hands after each autopsy with handwash containing bleach. However, some doctors remained unconvinced, seeing this as an attack on their medical competence. Today we know that handwashing had this miraculous-seeming effect as it broke the chain of contamination whereby the childbed fever's microbe was passed from the autopsied bodies to the doctor's hands and from there to the women in labour. Semmelweis believed that doctors transmitted the disease directly from the corpses to the women. Today the idea that infectious diseases are caused by microbes is so familiar to us that Semmelweis is often considered to be the precursor of the microbial theory of disease. This is false: for him and his contemporaries, a disease could be transmitted directly, and no one thought to investigate a cause other than contact with the sick person. It was microbiologists who identified microbes as the cause of diseases and set them as the target of treatments to cure them.

New scientific discoveries are often made not by scientists working directly on the subject of the discovery, or even in the domain to which it belongs, but through research on something entirely different, sometimes even in a completely different field. That was the case with micro-organisms and their role in the genesis of diseases. The

protagonist in this story was the young chemist Louis Pasteur. He was already known for his work on substances called tartrates; his hypothesis that two slightly different forms of tartrate could be each other's mirror image got him appointed director of the new science faculty in Lille, France. He was just over 30 years old. Quite soon he began work on fermentation – a spontaneous chemical transformation, first described many centuries ago, that produces alcohol as well as bread and certain cakes. At that time fermentation was already being used in industry, particularly in Lille and northern France. It was essential for the production of alcohol from beetroot juice.

Pasteur was interested in the complexity of these chemical transformations. After three years of observing fermentation, by chemical means and under the microscope, he was convinced that it was due to micro-organisms – "globules", as he called them. He wasn't the first to notice them, but he did identify them as the cause of fermentation. He discovered that fermentation takes place where micro-organisms find the food they need to thrive and propagate. Pasteur showed that every kind of fermentation is caused by a specific micro-organism, and that the rotting of organic matter, which we call putrefaction, is also caused by micro-organisms. He deduced from this, that micro-organisms, known since the invention of the microscope two centuries earlier but never identified as the cause of anything, their role unrecognized, fulfilled a function in nature that is essential to life: recycling the components of organic matter.

PROPAGATION. Transmission of a disease from one individual to another and beyond.

The link between fermentation, putrefaction and some diseases was not discovered by Pasteur. It had been uncovered much earlier. A disease like gangrene, which was fatal and often ensued after a wound, looked and smelled just like putrefaction.

From then on, as a result of Pasteur's work on fermentation, the presence of micro-organisms was noted more and more frequently in patients suffering from a variety of diseases. However, it still remained to be demonstrated that micro-organisms were the cause, not the consequence, of disease.

This was achieved not by Pasteur but by the German physician Robert Koch. He proved that anthrax*, a disease affecting both human and animals, like sheep or cattle, was due to a micro-organism – a bacterium. Koch isolated this bacterium from a sick animal, allowed it to multiply inside some cows' eyes, and then injected it into various species of animals who subsequently developed symptoms of infection by anthrax. He also showed that the anthrax bacterium could develop what we call spores, inactive forms that can survive for years before finding an environment in which to thrive, convert themselves back into bacteria and propagate. The existence of spores explains why the disease is often found in the meadows where it had thrived and

SPORE. Many bacteria can transform themselves into spores, which are capable of surviving several years in extreme conditions like heat, aridity and lack of food before transforming themselves back into bacteria and multiplying.

ravaged livestock several years earlier. Hence the name "cursed meadows".

Koch's experiment could be applied to any disease where the presence of micro-organisms had been detected and used to demonstrate that they were its cause.

Pasteur, who had not yet studied disease in humans, quickly following Koch's lead. But he did more than this: he demonstrated that we can protect ourselves against these diseases by injecting a weakened form of the micro-organism, thus introducing the revolutionary concept of vaccination. Pasteur first tried it out on chickens suffering from a disease called chicken cholera, then on anthrax, and finally on rabies*, a disease spread through the bites of infected dogs; it was quite rare, but people were terrified of it.

WEAKENED FORM. An infectious agent whose toxicity (ability to harm us) has been weakened by submitting it to a physical or chemical process.

Vaccination was known before Pasteur. The English physician Edward Jenner had noticed that cowhands who had been infected with a benign disease called cowpox were protected against smallpox*, a very serious disease. Others had remarked on this before him, but Jenner was the first to deduce that it provided a way of protecting an entire population. All one had to do was collect some of the liquid in the pustules that formed on the hands of cowhands infected with cowpox and inject it into others, who then went on to develop the disease and the pustules in their turn. This process could be repeated endlessly, creating vaccination chains. The method spread throughout Europe and led to a rapid fall in the number of smallpox cases.

However, cowpox was a unique case: there was no other human disease with a weakened form in animals. It was Pasteur who opened the way to developing vaccinations for many diseases where the microbe responsible for them had been identified. These microbes were cultivated in glass flasks, and the conditions in which the culture was grown, like the temperature, were tweaked until they were just right to render the micro-organism harmless without killing it.

In 1885, a little boy called Joseph Meister was bitten by a rabid dog in Alsace. As soon as he got to Paris, he was vaccinated against rabies in Pasteur's laboratory – even though Pasteur had not yet succeeded in identifying the microbe responsible for rabies. The boy was cured and the world rejoiced. Soon afterwards Pasteur was being hailed as a benefactor of humanity for discovering a method which – people hoped – might eradicate infectious diseases once and for all.

In 1889 two of Pasteur's students, Émile Roux and Alexandre Yersin, proved that diphtheria was caused by a toxic substance produced by a bacterium. A year later, in their Berlin laboratory, Emil Behring and Shibasaburo Kitasato found that an animal they had injected with the

ANTIBODY. A protein produced by our immune system which can recognise a specific target (a bacterium, a virus or another foreign substance), neutralise it and help eliminate it.

diptheria toxin had developed antitoxins in its serum a few days later. Today these antitoxins are called antibodies (Figure 1).

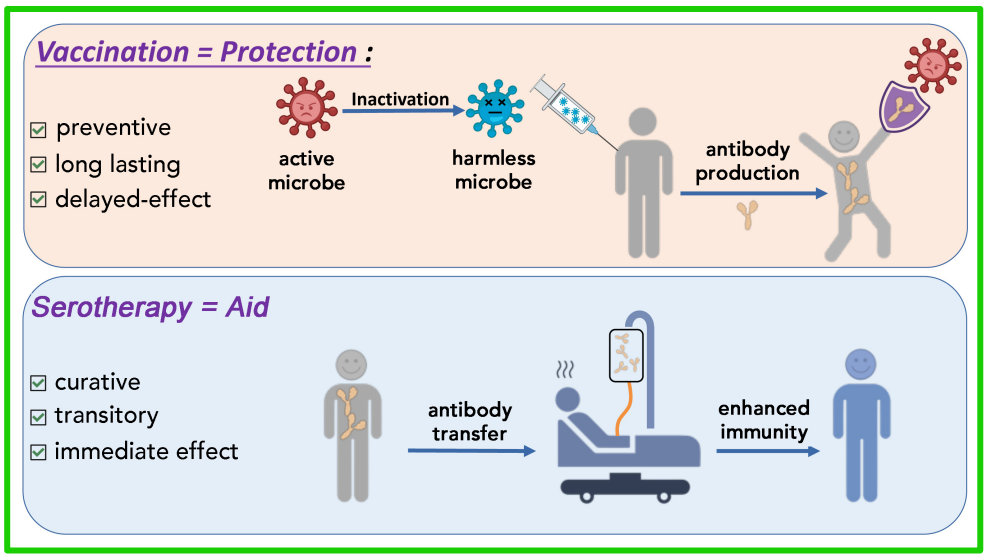


Figure 1. Vaccination and serotherapy: two ways to use antibodies to fight against microbes that make us ill. Vaccination protects against an infection that may happen in the future. Serotherapy is used to treat people who are already ill. In the 19th century serum from an animal immunized against the microbe responsible for the same disease was used, today we can also use human antibodies, from another person, vaccinated or recovered from the disease. Figure produced with BioRender.com.

Soon afterwards they showed that injecting serum containing these antitoxins into children with diptheria saved their life. In 1894 Émile Roux and his collaborators demonstrated the effectiveness of "anti-diptheria serotherapy", as it is called, on 500 children. Vaccination and serotherapy, along with antibiotics, which were discovered half a century later, became the only effective, but very powerful, weapons against infectious diseases.

INFECTIOUS DISEASE. An illness caused by a pathogenic organism, an infectious agent like a bacterium, a virus or a parasite.

## GLOSSARY OF INFECTIOUS DISEASES

TYPHOID. Illness that can be fatal, caused by bacteria transmitted by contaminated water or food.

DIPHTHERIA. Very serious illness in children, due to a toxin produced by bacteria. It is now very well controlled thanks to vaccination.

POLIO/POLIOMYELITIS. Highly contagious disease caused by a virus which invades the nervous system and can cause irreversible paralysis within a few hours

LEPROSY. Known and feared since Antiquity, it first affects the ends of the limbs and the face. People who showed signs of it were chased out of the villages. There are now very effective medications against it.

PUERPERAL FEVER (CHILDBED FEVER. A fatal illness which used to

occur in women a few days after childbirth. It was the result of contamination by a microbe, streptococcus, during labour.

BUBONIC PLAGUE. Disease, coming from the East, which reached Europe in the 14th century where it decimated more than a third of the population. It did not disappear definitively from Europe until the 18th century.

ANTHRAX. A fatal disease of herds caused by a bacterium; it can also affect humans.

RABIES. Contagious and fatal disease, of viral origin, which attacks the nervous system of mammals.

SMALLPOX. A human disease, often fatal, which leaves characteristic scars on the faces of its survivors. Completely eradicated throughout the world today.

## ACKNOWLEDGMENTS

The author wishes to thank Théo Paris and Sandrine Kinet for the illustrations

## FURTHER READING

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## ENGLISH VERSION

TRANSLATION: Agnieszka Kolakowska

EDITORS: Catherine Braun-Breton & Ula Hibner, Association Jeunes Francophones et la Science.

ACKOWLEDGMENTS. The editors thank the young reviewer Anaïs for her highly accurate and helpful comments on the linguistic style of the English version

SCIENCE MENTOR: Catherine Braun-Breton, Association Jeunes Francophones et la Science

CITATION: Morange M. 2024. It's the microbes! How we discovered that the villains were micro-organisms. Jeunes Francophones et la Science 2024 https://www.jeunesfrancophonesetlascience.fr/

CONFLICT OF INTEREST: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## YOUNG REVIEWERS

### CYRIL, AGE: 9

Hi, I am Cyril! I am highly interested by sciences, enjoy Legos and Star wars movies and love to play soccer.

### ANAÏS, AGE: 13

Hello, I'm Anaïs. I grew up loving rocks, horses, and all other animals. I ride at least 2-3 times a week and love spending time at the barn. I don't enjoy talking to people that much and prefer the company of animals. I have written the first 40 pages or so of a novel and have completed short stories.

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Michel Morange is an emeritus professor of biology at the École Normale Supérieure and Sorbonne-Université, Paris, France. His main research interest in biology is molecular developmental biology, as a historian and philosopher of science he has focused on the history and epistemology of the life sciences, from Pasteur to molecular biology. In this capacity, he directed the Centre Cavaillès d'Histoire et de Philosophie des Sciences.